REMARKS

Claims 1-35 are pending in the present application. Claims 15, 16, 31 and 32 have been withdrawn from consideration. Claims 1-14, 17-30 and 33-35 have been considered on the merits. In the present response, claim 1 and claim 17 have been amended. Support for these amendments can be found throughout the specification and claims as originally filed including at paragraph **[0034]**. The amendments to the claims do not add new matter and are otherwise proper. The Applicants respectfully request the Examiner enter the amendments in their entirety.

In the Office Action dated May 31, 2005, the Examiner continued to reject all of the claims based on the 35 U.S.C. § 103 grounds in view of cited references including U.S. Patent No. 6,197,061 ("Masuda *et al.*" or "the '061 Patent") as set forth previously in previously issued Office Actions. The Applicants believe that the claim amendments and the enclosed Declaration demonstrate that the rejection of the claims under 35 U.S.C. § 103 is improper and should be withdrawn for the following reasons.

I. Claim Amendments with Respect to "Culture Time"

In the Office Action dated May 31, 2005, the Examiner asserted "that the claims do not require a specific culture time." Claims 1 and 17 have been amended to recite "culturing isolated chondrogenic cells for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix but short enough such that the collagen fibrils in the cell-associated matrix do not become overly crosslinked, wherein the matrix loses roughly half of its proteoglycan content within 24 hours after treatment with IL-1 and loss of the proteoglycan content can be measured without the use of a radioactive agent." As such, the amended claims do require "a specific culture time."

Furthermore, there is no teaching or suggestion in the Masuda '061 Patent to prepare an engineered cartilage tissue that has been cultured as recited in the claims for used in methods for determining the effect of a test agent on the engineered cartilage tissue. With respect to culture time, the Masuda '061 Patent states:

> In an important aspect of the invention, the contents of collagen and of the pyridinoline crosslinks of collagen increase with time of culture. The crosslinks in particular show a dramatic increase in concentration after two weeks of culture. By keeping the length of the culture period relatively short, the collagen fibrils in the cell-associated matrix do not become overly crosslinked. A tissue that has good functional properties but is relatively deficient in crosslinks is easier to mold and more likely to become integrated within the host cartilage than a harder, crosslink-rich tissue.

As such, the Masuda '061 Patent teaches two general types of engineered tissue, including: (1) tissue that is "relatively deficient in crosslinks"; and (2) "harder, crosslink-rich tissue." However, there is no teaching in the Masuda '061 Patent to use tissue that has been cultured as recited in the present claims in methods for determining the effect of a test agent on the tissue (*i.e.*, tissue that has been cultured for a short enough period of time "such that the collagen fibrils in the cell-associated matrix do not become overly crosslinked").

For these reasons, the Applicants respectfully request that the Examiner reconsider and withdraw all the rejections discussed below which are based on the Masuda '061 Patent in view of the foregoing claim amendments and further in view of the Masuda Declaration discussed below.

II. Declaration Under 37 C.F.R. § 1.132 Submitted on March 23, 2005

The Applicants submitted a Declaration under 37 C.F.R. § 1.132 by Dr. Koichi Masuda on March 23, 2005 ("Masuda Declaration"), as part of a Request for Continued Examination ("RCE"). The Examiner has indicated that "such a declaration has not been received." As such, the Applicants have enclosed herewith a copy of the Masuda Declaration for the Examiner's consideration. The Applicants also have enclosed herewith a copy of the return receipt postcard that was submitted with the RCE, which lists the Masuda Declaration. The Examiner is requested to contact the Applicants' representative if a copy of the Masuda Declaration is not received with the present Amendment.

In the Masuda Declaration, Dr. Masuda discusses the Masuda *et al.* '061 Patent and in particular states:

> 5. ..."Unlike the artificial cartilage tissue in the present application, the tissue in the '061 Patent ***may be matured to a point*** where the tissue would not work in the invention of the [present] application because proteoglycan degradation would take several days."
>
> 6. ..."In the [present] application, because of the increased sensitivity, the proteoglycan degradation may be measured without the presen[ce] of radioactivity." Nothing in the tissue of the '061 patent suggests that this level of sensitivity can be obtained.
>
> 7. Our invention is now being used by a private sector company which has licensed our technology.

See Masuda Declaration, (emphasis added). As such, Dr. Masuda distinguishes the tissue used in the methods recited in the present claims from the tissue disclosed in the Masuda '061 Patent and further provides secondary considerations with respect to patentability of the claimed subject matter.

III. Kai *et al.* in view of the Masuda '061 Patent

In the Office Action, claims 1-8, 10, 14, 17-24, 26, 29-30 and 33 continue to be "rejected under 35 U.S.C. 103(a) as being unpatentable over Kai *et al.* (JP 2001 089390 A) in view of the Masuda '061 Patent. The Applicants continue to traverse this rejection. As stated in § 2143 of the M.P.E.P.,

> [t]o establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

First, the combination of Kai *et al.* and the Masuda '061 Patent fail to teach or suggest all of the claim limitations. Claims 1 and 17 have been amended to recite "culturing isolated chondrogenic cells for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix but short enough such that the collagen fibrils in the cell-associated matrix do not become overly crosslinked, wherein the matrix loses roughly half of its proteoglycan content within 24 hours after treatment with IL-1 and loss of the proteoglycan content can be measured without the use of a radioactive agent." Neither Kai *et al.* nor the Masuda '061 Patent suggest the use of engineered cartilage tissue that has been cultured as recited in the present claims in methods for determining the effect of a test agent on the tissue.

Further, the references fail to teach that proteoglycan degradation can be measured without the use of a radioactive agent. As set forth in the enclosed Masuda Declaration, it is only the present invention that provides for the measurement of proteoglycan degradation without radioactivity. *See* Masuda Declaration, paragraph 6. In fact, the Masuda '061 Patent teaches that radioactivity such as ^{35}S-Sulfate is used to measure proteoglycans. *See* Masuda '061 Patent, col. 11, line 7. Therefore, because Kai *et al.* and the Masuda '061 Patent, even in combination, fail to teach every limitation of the presently claimed methods, a *prima facie* case of obviousness has not been established and the Applicants respectfully submit that the 35 U.S.C. § 103 rejection be withdrawn and the claims be allowed to issue.

In addition, the Applicants once again submit that contrary to the Examiner's assertion, the rapid degradation of the cartilage tissue is not an inherent property of all of the engineered cartilage tissue disclosed by the Masuda '061 Patent. In response to the Applicants' argument that the rapid degradation is not inherent, the Examiner states that because the tissue in the present invention and the tissue in the Masuda '061 Patent are cultured in the same manner, the trait of rapid proteoglycan turnover must be inherent to both inventions. However, the Masuda '061 Patent specifically states that that "mechanical properties of the cartilage matrix can be controlled by increasing or decreasing the amount of

time that the cartilage tissue is cultured on the membrane[, and l]onger culture time will result in increased crosslink densities." *See* Masuda '061 Patent, col. 8, lines 41-45. *See also* Masuda Declaration, paragraph 5.

As the M.P.E.P. states under section 2112, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" (emphasis in original). The M.P.E.P. further states that:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.
>
> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

See M.P.E.P. § 2112 under the heading "Examiner Must Provide Rationale or Evidence Tending To Show Inherency" (emphasis in original).

In the Office Action, the Examiner implies that the Applicants are admitting that the rapid degradation of the tissue where the tissue loses roughly half of its proteoglycan content in 24 hours is inherent in the tissue of the Masuda '061 Patent. The Examiner appears to believe that the Applicants previous statement that "Applicants have recognized a previously unappreciated trait found in select samples of engineered cartilage tissues disclosed by the Masuda '061 Patent" supports this contention. However, the Examiner fails to appreciate that the Applicants are merely pointing out that rapid degradation of the tissue in the Masuda '061 Patent is only found in select (not all) samples. The Applicants' statement does not show that rapid degradation of the engineered cartilage tissue is inherent in all tissues disclosed by the Masuda '061 Patent, instead it demonstrates that the rapid degradation of the engineered

cartilage tissue is not inherent in all tissues disclosed by the Masuda '061 Patent. *See* Masuda Declaration, paragraph 5.

The engineered cartilage of the Masuda '061 Patent changes with time in culture. *See* Masuda Declaration, paragraph 5. Greater time in culture results in increased crosslink densities, making the tissue of the Masuda '061 Patent behave more like native cartilage tissue. *See* Masuda '061 Patent, col. 7, line 15. In this form, the tissue of the Masuda '061 Patent cannot be used in the present methods as native-like forms of the tissue of Masuda will take longer than 24 hours to produce 50% proteoglycan release. Thus, it is evident that how the tissue of the Masuda '061 Patent is cultured directly influences the time frame for proteoglycan release. Thus, rapid degradation is simply not a property that necessarily flows from the tissue of the Masuda '061 Patent. *See* Masuda Declaration, paragraph 5. The tissue disclosed in the Masuda '061 Patent is not like aspirin with a fixed composition and inherent properties. One must choose to culture the tissue in a specific way to obtain the property of rapid degradation for use in the claimed methods, and until the present invention, this particular response based on culture time was unknown. *See* Masuda Declaration, paragraph 5. Neither the Masuda '061 Patent nor Kai *et al* teach any such selection and use of engineered cartilage as recited in the present claims.

Based on the foregoing arguments, the Applicants respectfully submit that because the Kai *et al.* and the Masuda '061 Patent references, even when combined, fail to teach or suggest all the limitations recited in claims 1 and 17, the references cannot render claim 1 and claim 17 obvious. As claims 2-8, 10, 14, 18-24, 26, 29-30 and 33 all depend either directly or indirectly from claim 1 or claim 17, the cited art fails to establish a *prima facie* case of obviousness for these claims as well. Therefore, the Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) based on the combination of the Masuda '061 Patent and Kai *et al.* be withdrawn.

IV. Purchio *et al.* in view of the Masuda '061 Patent

The Examiner continues to reject claims 1-10, 14, 17-26, 33 and 35 "under 35 U.S.C. 103(a) as being unpatentable over Purchio *et al.* (US 5,902,741) in view of Masuda." Once again, the Applicants traverse this rejection.

Purchio *et al.* in combination with the Masuda '061 Patent fail to establish a *prima facie* case of obviousness. Even when taken together, Purchio *et al.* and the Masuda '061 Patent do not teach or suggest methods for determining the effect of a test agent on an engineered cartilage tissue that has been cultured "for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix but short enough such that the collagen fibrils in the cell-associated matrix do not become overly crosslinked, wherein the matrix loses roughly half of its proteoglycan content within 24 hours after treatment with IL-1 and loss of the proteoglycan content can be measured without the use of a radioactive agent," as recited in the amended claims.

Neither Purchio *et al.* nor the Masuda '061 Patent teach or suggest a method where proteoglycan content can be measured without the use of a radioactive agent. In fact, the Masuda '061 Patent teaches the use of ^{35}S-Sulfate, a radioactive agent, to measure proteoglycan content. Nothing in Purchio *et al.* suggest that non-radioactive methods may be used. As understood by the skilled artisan, there are numerous advantages to being able to measure proteoglycan content without the use of radioactive agents. For example, when non-radioactive agents are used, there is no need for laboratory personnel to be specially trained in the use of radioactivity. Moreover, the dangers of the uses of radioactivity, such as spills and accidental exposures can be eliminated. Thus, the skilled artisan clearly understands that inventions, such as the invention provided by the present patent application, which do not require the use of radioactivity but maintain similar measurement sensitivity are extremely advantageous. As neither of the references cited by the Examiner, either alone or in combination, teach or suggest an invention having the ability, as well as the advantages, of measuring proteoglycan content without the use of a radioactive agent, the references cannot make the present invention obvious. As this limitation is present in the independent claims, the references cited by the Examiner also fail to make the dependent claims obvious.

Therefore, the Applicants respectfully request the Examiner withdrawn the 35 U.S.C. § 103 rejection of claims 1-10, 14, 17-26, 33 and 35 and allow the claims to issue.

Furthermore, contrary to the Examiner's assertion, rapid degradation is not an inherent feature of the all the engineered cartilage tissue of the Masuda '061 Patent. *See* Masuda Declaration, paragraph 5; and discussion above. The Applicants respectfully submit that because the Purchio *et al.* and the Masuda '061 Patent references, even when combined, fail to teach or suggest all the limitations recited in claims 1 and 17, the references cannot render claim 1 and claim 17 obvious. As claims 2-10, 14, 18-26, 33 and 35 all depend either directly or indirectly from claim 1 or claim 17, the art cited by the Examiner also fails to teach and every element of these claims. Thus, the Applicants respectfully request the Examiner withdraw the rejection and allow claims 1-10, 14, 17-26, 33, and 35 to issue.

V. Saito *et al.* in view of the Masuda '061 Patent

In the final Office Action, claims 1-8, 17-24, 29-30 and 35 were "rejected under 35 U.S.C. 103(a) as being unpatentable over Saito *et al.* in view of the Masuda '061 Patent" The Applicants continue to traverse this rejection.

Yet again, a *prima facie* case of obviousness has not been satisfied as the combination of Saito *et al.* with the Masuda '061 Patent does not teach or suggest methods for determining the effect of a test agent on an engineered cartilage tissue that has been cultured "for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix but short enough such that the collagen fibrils in the cell-associated matrix do not become overly crosslinked, wherein the matrix loses roughly half of its proteoglycan content within 24 hours after treatment with IL-1 and loss of the proteoglycan content can be measured without the use of a radioactive agent," as recited in the amended claims.

Neither Saito *et al.* nor the Masuda '061 Patent provide for the measurement of proteoglycan content without the use of a radioactive agent. In fact, as set forth above, the Masuda '061 Patent teaches the use of ^{35}S-Sulfate to measure proteoglycan content. Moreover, nothing in Saito *et al.* contradict the teaching of the use of a radioactive agent nor suggest that proteoglycan content can be measured without the use of a radioactive agent. For

the reason that neither Saito *et al.* nor the Masuda '061 Patent, either alone or in combination, teach or suggest the use of a non-radioactive method to measure the amount of proteoglycan, the two references cannot make obvious the claims of the present invention. Therefore, the Applicants respectfully request the Examiner withdraw the 35 U.S.C. § 103 rejection based on the Masuda '061 Patent and Saito *et al.*

In addition, as set forth above, the use of an engineered tissue cultured to be rapidly degraded is not inherent to all the engineered cartilage tissue of the Masuda '061 Patent. *See* Masuda Declaration, paragraph 5. Furthermore, because Saito *et al.* lack any discussion of a tissue or procedure demonstrating this trait, Saito *et al.* fail to cure this deficiency. As this element is not taught in either reference cited by the Examiner, the references cannot render the present claims obvious even if the references are taken together. Thus, a *prima facie* case of obviousness has not been established and the Examiner should withdraw the 35 U.S.C. § 103 rejection.

Moreover, there is no motivation to combine the Saito *et al.* and the Masuda '061 Patent references. Indeed, Saito *et al.* teach away from combining the references because, by definition, the cartilage explant of Saito *et al.* is a non-engineered tissue that is obtained directly from an animal. As those of ordinary skill in the art will appreciate, it would be impossible to employ this "natural" tissue with the methods of the Masuda '061 Patent while still maintaining the essential natural character required by culture of an explant. For example, the engineered cartilage tissue used in the present invention is highly homogenous, in contrast to the "natural" cartilage tissue in cartilage explants such as those used in Saito *et al.* Although the use of engineered cartilage tissue may be advantageous in many circumstances, in some cases, such as when experimentation centers around the response of an individual animal to a test agent, it may be more advantageous to use explant culture. Explants are particularly useful when intervariability between animals is irrelevant. Therefore, because whether a "natural" cartilage tissue or an engineered cartilage tissue is preferable may change depending on the particular application, the two types of tissue are not interchangeable as suggested by the Examiner.

As such, the combination of Saito *et al.* and the Masuda '061 Patent does not establish a *prima facie* case of "obviousness" with respect to the pending claims. The Applicants respectfully request that the 35 U.S.C. § 103(a) rejection based on these art references be reconsidered and withdrawn.

VI. Huch *et al.* in view of the Masuda '061 Patent

The Examiner continues to reject claims 1-11, 17-27 and 29-30 "under 35 U.S.C. 103(a) as being unpatentable over Huch *et al.* (1997) in view of the Masuda '061 Patent" This rejection must also fail for the reasons discussed above, and, in particular, those reasons relating to the combination of Kai *et al.* and the Masuda '061 Patent.

Huch *et al.* combined with the Masuda '061 Patent does not teach or suggest all of the claim limitations in the pending claims. Neither Huch *et al.* nor the Masuda '061 Patent teach or suggest methods for determining the effect of a test agent on an engineered cartilage tissue that has been cultured "for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix but short enough such that the collagen fibrils in the cell-associated matrix do not become overly crosslinked, wherein the matrix loses roughly half of its proteoglycan content within 24 hours after treatment with IL-1 and loss of the proteoglycan content can be measured without the use of a radioactive agent," as recited in the amended claims.

Rather, Huch *et al.* and the Masuda '061 Patent teach the quantification of proteoglycans using ^{35}S-Sulfate, a radioactive marker. As set forth in Huch *et al.*, "incorporation of ^{35}S-Sulfate into proteoglycans was quantified during the last 4 hours of culture and reported as counts per minute per μg DNA." *See* Huch *et al.* page 2157, col. 1. Neither Huch *et al.* nor the Masuda '061 Patent teach or suggest either the disadvantages of using a radioactive marker or that non-radioactive methods will be sensitive enough to measure proteoglycan content. As Huch *et al.* and the Masuda '061 Patent, even in combination, fail to disclose every element of the independent claims of the present invention, the references cannot render the currently pending claims obvious. Therefore, The

Applicants respectfully submit that the 35 U.S.C. § 103 rejection is improper and should be withdrawn.

In addition, neither Huch *et al.* nor the Masuda '061 Patent teach or suggest a cartilage tissue that exhibits rapid degradation. In fact, degradation of chondrocyte cells similar to the cells in Huch *et al.* occurs at a much slower pace than degradation of the engineered tissue of the present invention. *See* Aydelotte *et al.*, Articular Cartilage and Osteoarthritis 237, FIG. 2 (1992) (previously submitted). Thus, using the cartilage of Huch *et al.* with the methods of the Masuda '061 Patent, in the manner suggested by the Examiner, results in an assay with a different and slower speed of cartilage degradation beyond the scope of the present claims. The rapid tissue degradation of the present claims lends itself to high throughput screening, which is advantageous for many reasons. Additionally, as set forth above, the rapid degradation is not an inherent quality of the all the engineered cartilage tissue of the Masuda '061 Patent.

Because even when combined, Huch *et al.* and the Masuda '061 Patent fail to teach all the limitations of the present invention, the combination of Huch *et al.* and the Masuda '061 Patent fails to establish a proper *prima facie* case of "obviousness." Thus, the Applicants respectfully request the Examiner reconsider and withdraw this rejection.

VII. Lansbury *et al.* in view of the Masuda '061 Patent

Finally, in the final Office Action claims 1-8, 10, 14, 17-24, 26 and 33 were once again "rejected under 35 U.S.C. 103(a) as being unpatentable over Lansbury *et al.* (WO 94/28889) in view of the Masuda '061 Patent" This combination also does not establish a *prima facie* case of obviousness. Neither Lansbury *et al.* nor Masuda *et al.* teach or suggest methods for determining the effect of a test agent on an engineered cartilage tissue that has been cultured "for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix but short enough such that the collagen fibrils in the cell-associated matrix do not become overly crosslinked, wherein the matrix loses roughly half of its proteoglycan content within 24 hours after treatment with IL-1 and loss of the proteoglycan content can be measured without the use of a radioactive agent," as recited in the amended claims.

In contrast to providing methods wherein proteoglycan content can be measured without the use of radioactivity, both Lansbury *et al.* and the Masuda '061 Patent describe the measurement of proteoglycans using ^{35}S-Sulfate. *See* Lansbury *et al.*, page 24, line 16. Lansbury *et al.* even go as far as to include another radioactive method that can be used to measure proteoglycan content. *See* Lansbury *et al.*, page 25, line 35. Because both Lansbury *et al.* and the Masuda '061 Patent teach away from the use of non-radioactive methods to measure proteoglycan content, Lansbury *et al.* and the Masuda '061 Patent fail to teach or suggest every limitation of the pending claims. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

Because a *prima facie* case of obviousness is not established, the Applicants respectfully request the Examiner reconsider and withdraw this rejection.

VIII. Conclusion

In view of the above remarks, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. Examiner Davis is invited to contact the undersigned at the number listed below if she believes such would be helpful in advancing the application to issue.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-2350. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-2350. If any extensions of time are needed for timely acceptance of papers submitted herewith, the applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-2350.

Respectfully submitted,

Date 10/31/2005

By _____

FOLEY & LARDNER LLP
Customer Number: 23524

M. Scott McBride
Attorney for the Applicants
Registration No. 52,008
Telephone: (414) 297-5529
Facsimile: (414) 297-4900